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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/722,602	11/27/2000	Frances H. Arnold	9373/1G811US1	5781

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EXAMINER

PAK, YONG D

ART UNIT	PAPER NUMBER
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1652

DATE MAILED: 07/05/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/722,602

Applicant(s)

ARNOLD ET AL.

Examiner

Yong D. Pak

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 04 April 2005.
2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 63-90,93,94,97-111 and 113-127 is/are pending in the application.
4a) Of the above claim(s) _____ is/are withdrawn from consideration.
5) ☒ Claim(s) 111 is/are allowed.
6) ☒ Claim(s) 63-90,93,94,97-110 and 113-127 is/are rejected.
7) ☐ Claim(s) _____ is/are objected to.
8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 12/6/04
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____

DETAILED ACTION

This application is a CIP of 09/571,553.

The amendment filed on April 4, 2005, amending claims 63-87, 89, 93, 97, 99, 101, 103, 105, 107, 109 and 116-125 and adding claims 126-127, has been entered.

Claims 63-90, 93, 94, 97-111 and 113-127 are pending and are under consideration.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on December 16, 2004 is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Response to Arguments

Applicant's amendment and arguments filed on April 4, 2005, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. Specifically, Examiner has withdrawn the previous rejection of claims 63-90, 93-94 and 97-110 under 35 U.S.C. 112, 1st paragraph and a new rejection of claims 63-64, 66-90, 93-94, 97-102, 105-106 and 109-110 under 35 U.S.C. 112, 1st paragraph is set forth below.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 63 and 64 and claims 65-82 and 113-114 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 63 and 64 recite the phrase "galactose oxidase variant comprising SEQ ID NO:10". The metes and bounds are not clear in the context of the claims. SEQ ID NO:10 is the wild type galactose oxidase from *D. dendroides*. It is not clear to the Examiner how a galactose oxidase variant can comprise of SEQ ID NO:10. Therefore, it is unclear from the specification or from the claim as to what applicants mean by the above phrase.

Claims 83, 87, 89, 93, 97, 99, 101, 105 and 109 and claims 84-86, 88, 90, 94, 98, 99, 102, 106, 110, 116-122, 124 and 125 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 83, 87, 89, 93, 97, 99, 101, 105 and 109 recite the phrase "galactose oxidase variant derived from wild-type D. derived from a wild-type *D. dendroides* galactose oxidase". The metes and bounds of this phrase are not clear to the Examiner. Literally, while the term "derived" means "to isolate from or obtain from a

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source", the above term could also mean "to arrive at by reasoning i.e., to deduce or infer" or also as "to produce or obtain from another substance". Therefore, it is not clear to the Examiner either from the specification or from the claims as to what applicants mean by the above phrase. It is not clear to the Examiner whether the galactose oxidase variant "derived from wild type *D. dendroides*" encompasses a single specific enzyme (SEQ ID NO:11-21), or whether it encompasses recombinants, variants and mutants of any galactose oxidase from any source and labeled as a galactose oxidase variant "derived from wild type *D. dendroides*". As applicants have not provided a definition for the above phrase, Examiner has interpreted the claims broadly to mean that a galactose oxidase variant "derived from wild type *D. dendroides*" encompasses polypeptides which are recombinants, variants or mutants of any galactose oxidase. Examiner has given the same interpretation while considering the claims for all other rejections.

Claims 83, 87, 89, 93, 97, 99, 101, 105, 109 and 116-125 and claims 84-86, 88, 90, 94, 98, 99, 102, 106 and 110 depending therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 83, 87, 89, 93, 97, 99, 101, 105, 109 and 116-125 recite the phrase "*D. dendroides* has accession no. ATCC46032". The metes and bounds of this phrase are not clear to the Examiner. Without the recitation of the SEQ ID NO of the galactose oxidase of *D. dendroides* having accession no. ATCC46032, it is not clear to the

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Examiner which amino acid position in a galactose oxidase sequence the recited amino acids are referring to or how to interpret the percent homology between the variant and the wild type galactose oxidase. Examiner suggests direct reference to the SEQ ID NO.

Claims 103 and 107 and claims 104 and 108 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 103 and 107 recite the phrase "corresponding" to amino acid positions. SEQ ID NO:10 is not the wildtype sequence but a variant of the wildtype. It is not clear to the Examiner as to how those skilled in the art can determine as to which amino acid on a variant "corresponds to" which amino acid in the wild type. A perusal of the specification did not provide any guidance, rendering the claim unclear. Examiner suggests deleting the phrase of making direct reference to the amino acid position.

In response to the previous Office Action, applicants have requested withdrawn of the rejection because applicants have amended the claims to remove "corresponding to". Examiner respectfully disagrees. The phrase "corresponding to" has not been removed from claims 103 and 107. Hence, the rejection is maintained.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 63-64, 66-90, 93-94, 97-102, 105-106 and 109-110 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a galactose oxidase variant of SEQ ID NO:10 consisting of the recited amino acid mutations, does not reasonably provide enablement for a galactose oxidase variant of SEQ ID NO:10 comprising the recited the amino acid mutations and any other amino acid mutations. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. (See rejection of the phrase "derived" under 35 U.S.C. 112, 2nd paragraph above).

Claims 63-64, 66-90, 93-94, 97-102, 105-106 and 109-110 are drawn to galactose oxidase variants of SEQ ID NO:2 or galactose oxidase "derived" from *D. dendroides*, which includes any variants, mutants or recombinants of a galactose oxidase from *D. dendroides*, comprising the recited amino acid mutations and any other

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amino acid mutations. Therefore, these claims are drawn to galactose oxidase variants having any structure, other than having the recited amino acid mutations.

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polypeptides encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to galactose oxidase variants of SEQ ID NO:10 consisting of the recited amino acid mutations.

It would require undue experimentation of the skilled artisan to make and use the claimed polypeptides. In view of the great breadth of the claim, amount of experimentation required to make the claimed polypeptides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure, the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polypeptides encompassed by the claims.

While enzyme isolation techniques, recombinant and mutagenesis techniques are known, and it is routine in the art to screen for multiple substitutions or multiple modifications as encompassed by the instant claims, the specific amino acid positions

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within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass modifications of any or all amino acid mutations of a galactose oxidase of SEQ ID NO:10 or a galactose oxidase derived from *D. dendroides*, which includes any or all recombinants, mutants or variants of a galactose oxidase from *D. dendroides*, because the specification does not establish: (A) regions of the polypeptide structure which may be modified without affecting galactose oxidase activity; (B) the general tolerance of galactose oxidase to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including galactose oxidase variants with an enormous number of amino acid modifications of SEQ ID NO:10 or any galactose oxidase, including any variants, mutants or recombinants of a galactose oxidase from *D. dendroides*. The scope of the claims must bear a reasonable correlation with the scope

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of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of the galactose oxidase variants having catalytic activity is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In response to the previous Office Action, applicants have traversed the above rejection. Applicants argue that the ability to mutagenize and screen hundreds, if not thousands of variants can be accomplished easily and rapidly without undue experimentation. Examiner respectfully disagrees. The claims are drawn to galactose variants comprising of the recited amino acid mutations and any other amino acid mutations. Therefore, the scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polypeptides encompassed by the claims. As discussed above, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a specific knowledge of and guidance with regard to which specific amino acids in the protein's sequence, can be modified such that the modified polypeptide continues to have said claimed activity. It is this specific guidance that applicants do not provide. Without specific guidance, those skilled in the art will be subjected to undue experimentation of making and testing each of the enormously large number of mutants that results from such experimentation. While the art may teach in general the structure of a galactose oxidase, conserved amino acid sequences, and etc,

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such teachings will not reduce the burden of undue experimentation on those of ordinary skill in the art. Hence the rejection is maintained.

Allowable Subject Matter

Claim 111 is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.


Any inquiry concerning this communication or earlier communications from the examiner should be directed to Yong Pak whose telephone number is 571-272-0935. The examiner can normally be reached 6:30 A.M. to 5:00 P.M. Monday through Thursday.

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If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned are 571-273-8300 for regular communications and 703-872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.

Yong D. Pak
Patent Examiner 1652



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